Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (Currently amended) A transgenic ~~nonhuman animal~~ mouse comprising at least one nonfunctional allele of a beta-secretase-1 (BACE-1) gene, wherein the allele is rendered nonfunctional by deletion of exons 4-8.

Claim 2 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 1 that is homozygous for the allele.

Claims 3-4 (Cancel)

Claim 5 (Currently amended) The transgenic ~~animal~~ mouse of claim 1, wherein the ~~animal~~ mouse or an ancestor thereof was produced by homologous recombination between an endogenous allele of the gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the gene for the construct to recombine with the endogenous allele introducing the positive selection marker into the endogenous allele and rendering it nonfunctional.

Claim 6. (Currently amended) The transgenic ~~animal~~ mouse of claim 1, wherein the ~~animal~~ mouse or an ancestor thereof was produced by homologous recombination between an endogenous allele of the gene and a construct containing a positive selection marker flanked by segments showing

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sufficient sequence relatedness to the gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites, whereby the construct recombines with the endogenous gene introducing the positive selection marker and frt recombination sites into the endogenous allele, and the frt recombination sites undergo recombination with each other thereby excising DNA between the flp recombination sites resulting in a deleted nonfunctional form of the endogenous allele.

Claims 7-8 (Canceled)

Claim 9 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 1, wherein the allele is rendered nonfunctional by homologous recombination with a targeting vector comprising a lambda KOS genomic clone of BACE-1.

Claims 10 -12 (Canceled)

Claim 13 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 1, further comprising a transgene comprising a mutation in the APP gene associated with familial Alzheimer's disease.

Claim 14 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 13, wherein the transgene comprises a mutation at codons 595 and 596 of human APP695, or an isoform or fragment thereof, wherein the amino acid residues at

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positions corresponding to positions 595 and 596 are asparagine and leucine, respectively.

Claim 15 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 13, wherein the transgene comprises a mutation at codon 717 of APP770 or an isoform or fragment of APP770 having a mutant amino acid residue at position 717.

Claim 16 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 13, wherein the mutant amino acid residue is isoleucine, phenylalanine or glycine.

Claim 17 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claims 13, wherein the ~~animal~~ mouse is homozygous for the non-functional allele.

Claim 18 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 13, wherein the ~~animal~~ mouse is heterozygous for the transgene.

Claim 19 (Currently amended) A cortical cell culture derived from the transgenic ~~animal~~ mouse of claim 1.

Claim 20 (Previously presented) The cortical cell culture of claim 19, wherein the cell culture is a primary cell culture.

Claim 21 (Previously presented) The cortical cell culture of claim 19, wherein the cell culture comprises a detectable amount of a peptide recognized by an antibody that recognizes residues 13-28 of Aβ.

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Claim 22 (Currently amended) A method for screening for an inhibitor of the production by a protease other than ~~beta-secretase ("non-beta-secretase protease")~~ BACE-1 of a peptide recognized by an antibody that recognizes residues 13-28 of Aβ comprising

exposing a transgenic ~~nonhuman animal comprising at least one nonfunctional~~ mouse lacking a functional allele of a beta-secretase-1 (BACE-1) gene or a cortical cell culture derived therefrom to an agent, and

detecting the peptide produced in the transgenic ~~animal~~ mouse or cell culture exposed to the agent,

wherein a reduced amount of peptide produced in the exposed transgenic ~~animal~~ mouse or cell culture relative to a transgenic ~~animal~~ mouse or cell culture which has not been exposed to the agent is indicative of inhibitory activity.

Claim 23 (Previously presented) The method of claim 22, wherein a cortical cell culture is exposed to the agent.

Claim 24 (Previously presented) The method of claim 22, wherein the cortical cell culture is a primary cell culture.

Claim 25 (Currently amended) A method of analyzing potential side-effects for an inhibitor of beta-secretase, comprising:

exposing a transgenic ~~nonhuman animal~~ mouse comprising at least one nonfunctional allele of a beta-secretase-1 (BACE-1) gene or a cortical cell culture

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	derived therefrom to an inhibitor of beta secretase; and measuring whether there is a change in the level of at least one component of the transgenic ~~animal~~ mouse or cortical cell responsive to the administration of the inhibitor; wherein a change in the level of at least one component indicates a potential side effect.
Claim 26 (Previously presented)	The method of claim 25, wherein the measuring step measures changes in the levels of a plurality of mRNA species.
Claim 27 (Currently amended)	~~An~~ A mouse embryonic stem cell comprising at least one nonfunctional allele of a beta-secretase-1 (BACE-1) gene, wherein the allele is rendered nonfunctional by deletion of exons 4-8.
Claim 28 (Currently amended)	The mouse embryonic stem cell of claim 27 that is homozygous for the allele.
Claim 29 (Cancel)	
Claim 30 (Currently amended)	The mouse embryonic stem cell of claim 27 produced by homologous recombination with a targeting vector designed in a way that, upon homologous recombination, exons 4 to 8 of the BACE-1 gene are flanked with FLP recombinase target sites (frt sites).
Claim 31 (Currently amended)	The mouse embryonic stem cell of claim 30, produced by homologous recombination with a

targeting vector designed in a way that, with respect to the genomic locus, the 5' region of homology covered 4.5 kb and the 3' region 4.3 kb until the third frt site, and an additional 1.5 kb further 3'.

Claim 32 (Currently amended) The mouse embryonic stem cell of claim 27 that is homozygous for a nonfunctional allele lacking exons 4-8 of BACE-1.

Claim 33 (Currently amended) The mouse embryonic stem cell of claim 27, produced by homologous recombination with a first targeting vector that introduces a neomycin resistance gene in the BACE-1 gene and with a second targeting vector that replaces the neomycin resistance gene with a hygromycin resistance gene cassette.

Claim 34 (Currently amended) A blastocyst formed by differentiation of ~~an~~ a mouse embryonic stem cell as described in claim 27.

Claim 35 (Currently amended) A method for generating a transgenic ~~nonhuman animal~~ mouse comprising at least one nonfunctional allele of a beta-secretase-1 (BACE-1) gene, the method comprising:

introducing at least one genetic construct into ~~an~~ a mouse embryonic stem cell line, the genetic construct comprising a positive selection marker flanked by segments showing sufficient sequence relatedness to the BACE-1 gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites;

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screening for cells in which recombination has occurred between the genetic construct and the endogenous gene;

injecting the mouse embryonic stem cells which have undergone recombination into blastocysts ~~from a nonhuman animal~~ to generate chimeric ~~nonhuman animals~~ mice;

breeding the chimeric ~~nonhuman animals~~ mice with ~~nonhuman animals~~ mice of the type which provided the blastocysts to generate the chimeric ~~nonhuman animals~~ mice to generate ~~nonhuman animals~~ mice heterozygous for the nonfunctional allele of BACE-1; and

breeding the ~~nonhuman animals~~ mice heterozygous for the nonfunctional allele of BACE-1 with ~~nonhuman animals~~ mice transgenic for flp recombinase resulting in a nonfunctional form of the endogenous BACE-1 allele.

Claim 36 (Previously presented) The method of claim 35, wherein the allele is rendered nonfunctional by deletion of at least a segment from exon 1.

Claim 37 (Previously presented) The method of claim 35, wherein the allele is rendered nonfunctional by deletion of exons 4-8.

Claim 38 (Currently amended) A transgenic ~~nonhuman animal~~ mouse comprising at least one nonfunctional allele of a beta-secretase-1 (BACE-1) gene, wherein the ~~animal~~ mouse or an ancestor thereof was produced by homologous

recombination between an endogenous allele of the gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites, whereby the construct recombines with the endogenous gene introducing the positive selection marker and frt recombination sites into the endogenous allele, and the frt recombination sites undergo recombination with each other thereby excising DNA between the flp recombination sites resulting in a deleted nonfunctional form of the endogenous allele.

Claim 39 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 38 that is homozygous for the allele.

Claims 40-41 (Cancel)

Claim 42 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 38, wherein the allele is rendered nonfunctional by deletion of at least a segment of an exon of the gene.

Claim 43 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 38, wherein the allele is rendered nonfunctional by deletion of at least a segment from exon 1.

Claim 44 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 38, wherein the allele is rendered nonfunctional by a 165 base pair deletion of exon 1 starting from 2 basepairs

past the initiating methionine and extending through the end of exon 1 replaced with an expression cassette in the targeting vector electroporated into 129 ES cells to generate the transgenic ~~nonhuman animal~~ mouse.

Claim 45 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 38, wherein the allele is rendered nonfunctional by deletion of exons 4-8.

Claim 46 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 38, further comprising a transgene comprising a mutation in the APP gene associated with familial Alzheimer's disease.

Claim 47 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 46, wherein the transgene comprises a mutation at codons 595 and 596 of human APP695, or an isoform or fragment thereof, wherein the amino acid residues at positions corresponding to positions 595 and 596 are □sparagines and leucine, respectively.

Claim 48 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 46, wherein the transgene comprises a mutation at codon 717 of APP770 or an isoform or fragment of APP770 having a mutant amino acid residue at position 717.

Claim 49 (Currently amended) The transgenic ~~nonhuman animal~~ mouse of claim 46, wherein the mutant amino acid residue is isoleucine, phenylalanine or glycine.

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Claim 50 (Currently amended) A cortical cell culture derived from the transgenic ~~animal~~ mouse of claim 38.

Claim 51 (Previously presented) The cortical cell culture of claim 38, wherein the cell culture is a primary cell culture.

Claim 52 (Previously presented) The cortical cell culture of claim 38, wherein the cell culture comprises a detectable amount of a peptide recognized by an antibody that recognizes residues 13-28 of Aβ.

Claim 53 (New) The cortical cell culture of claim 21, wherein the peptide recognized by an antibody that recognizes residues 13-28 of Aβ is β-amyloid.

Claim 54 (New) The method of claim 22, wherein the peptide recognized by an antibody that recognizes residues 13-28 of Aβ is β-amyloid.

Claim 55 (New) The cortical cell culture of claim 52, wherein the peptide recognized by an antibody that recognizes residues 13-28 of Aβ is β-amyloid.

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